
# The management of severe portopulmonary hypertension in patients undergoing liver transplantation



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**Abstract**

Aim: Severe portopulmonary arterial hypertension (PoPAH) is still considered a contraindication for liver transplantation at most transplant centers due to its high morbidity and mortality rate. However, with the advances in specific pulmonary arterial hypertension therapy and transplantation surgery, the outcomes of these patients are significantly improving. Material and Method: All patients who were candidates for liver transplantation underwent a standardized pre-operative pulmonary and cardiac evaluation. Assessment and staging severity of PoPAH was based on transthoracic Doppler echo-cardiographic examination. Severe pulmonary hypertension was defined as mean pulmonary artery pressure > 45 mm Hg. A standardized preoperative bridging therapy and intraoperative pulmonary hypertension management were performed in patients with severe PoPAH. Because of the therapeutic potential of inhaled nitric oxide as a selective pulmonary vasodilator, it was used perioperatively for all patients in combination with sildenafil. Clinical and demographic variables and laboratory data were noted. Results: Among 505 patients who underwent liver transplantation, 5 whose mean pulmonary artery pressure > 45 mm Hg were enrolled. While 2 of 5 patients received cadaveric livers, the other 3 were living donor transplantation, and one of them was pediatric. There was no perioperative mortality. During our follow-up only 1 patient died three years after transplantation because of coronary artery disease. Discussion: We recommend that liver transplantation should not be denied to all patients with severe PoPAH if they do not have right ventricular dysfunction. With bridging therapy, advanced anesthetic and surgical management, patients with severe PoPAH can be candidates for liver transplantation.

**Keywords**

Portopulmonary Hypertension; Liver Transplantation; Nitric Oxide; Sildenafil

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## Introduction

Portopulmonary arterial hypertension (PoPAH) is a rare but severe pulmonary vascular complication of end-stage liver disease. With the use of mean pulmonary artery pressure (mPAP), the disease can be classified into three stages as shown in Table 1 (1). While survival is very low without medical treatment or liver transplantation (2,3), with the advances in specific pulmonary arterial hypertension (bridging therapy) therapy and transplantation surgery, outcomes are significantly improving.

PoPAH is characterized by increased resistance to pulmonary arterial flow due to pulmonary endothelial and smooth muscle proliferation, and in situ thrombosis (4). Unlike PoPAH, hepatopulmonary syndrome (HPS), which is the other vascular complication of liver disease, is caused by hyperdynamic circulation, intrapulmonary shunts, and pulmonary vasodilatation. Medical treatment cannot cure these two conditions and they have prognostic significance in relation to liver transplantation outcomes. While HPS usually resolves after liver transplantation, the response of PoPAH is unpredictable (1). But it is known that without medical intervention, the 5-year survival rate is approximately 5.3% to 8.5% (4,5) in PoPAH patients.

Because of high perioperative morbidity and mortality related to right heart failure, the severe form of PoPAH has been considered a contraindication to liver transplantation (3,6,7). It is said that without prior attempts to reduce pulmonary pressure, moderate PoPAH causes an estimated 50% mortality rate after liver transplantation while its severe form may result in a 100% mortality rate (4,8). İn this study we report on our severe PoPAH patients undergoing liver transplantation.

## Material and Method

After obtaining approval from the hospital ethics committee, the records of pediatric and adult patients with chronic liver disease who underwent liver transplantation at our center between 2015 and 2018 were retrospectively evaluated. Patient charts and an electronic medical recording system were used for data collection. All patients underwent a standardized preoperative pulmonary and cardiac evaluation. We obtained assessment and staging severity of PoPAH based on transthoracic Doppler echo-cardiographic (TTE) examination which was done according to recommendations of The American Association for the Study of Liver Disease and the International Liver Transplantation Society (9). Severe pulmonary hypertension was defined as mean pulmonary artery pressure > 45 mm Hg. In some of the patients with severe PoPAH, right heart catheterization was conducted as a confirmatory test.

Table 1. Staging of severity of portopulmonary hypertension

| Stage | Mean pulmonary artery pressure (mm Hg) |
|---|---|
| Mild | 25-35 |
| Moderate | 35-45 |
| Severe | >45 |

Table 2. Preoperative characteristic features of the patients

| | Age at transplant | Gender | BMI | MELD PELD | ASA | Primary diagnosis | Comorbid disease | Living donor/ cadaveric |
|---|---|---|---|---|---|---|---|---|
| Patient1 | 46 | Male | 21.5 | 22 | 3 | Alcoholic | _ | Living donor |
| Patient2 | 35 | Female | 22.4 | 24 | 3 | NASH+HCC | DM, HT | Living donor |
| Patient3 | 7 | Male | 15.0 | 16 | 3 | Hyperoxaluria | ESRD | Living donor |
| Patient4 | 59 | Male | 31.6 | 20 | 3 | NASH | CAD | Cadaveric |
| Patient5 | 43 | Male | 28.4 | 20 | 3 | HBV | _ | Cadaveric |

Among 505 patients who underwent liver transplantation, 5 whose mean pulmonary artery pressure > 45 mm Hg were enrolled. Clinical and demographic variables and laboratory data were noted. We also obtained data including etiology of disease prior to transplantation, comorbid diseases, routine cardiologic and pulmonary assessment findings, type of medications for preoperative bridging therapy and intraoperative pulmonary hypertension management, intraoperative blood product usage, intraoperative inotrope/vasopressor usage, duration of anhepatic phase and surgery, pre- and postoperative TTE examination findings, postoperative complications, length of hospital/intensive care unit stay, and perioperative and one-year mortality.

Because severe pulmonary hypertension is accepted as a contraindication for undergoing transplantation at most transplant centers, as part of our hospital's routine practice the recipients were informed in detail about the preoperative process before the operation. The potential risks, success, and morbidity-mortality rates were explained to both the recipient and family. All patients received a standardized anesthetic regimen and all operations were performed by the same surgical team using a standardized technique.

In the operating room a standard monitoring regimen including invasive arterial pressure, central venous pressure, peripheral oxygen saturation, 5-lead electrocardiogram, and end-tidal CO2 monitoring was performed. Additionally, cardiac output monitoring with Pulse Contact Cardiac Output (PiCCO) was applied because there is an unpredictable increase in cardiac output causing additional stress on right ventricul during reperfusion. While in liver transplantation, major changes in pulmonary hemodynamics with reperfusion remain a clinical challenge (10) and pulmonary artery catheter monitoring is the usual standard of care. In our study, intraoperative management of PoPAH was aided by using PiCCO to assess right ventricle function. Based on our PiCCO monitoring, interventions were performed if necessary.

## Results

Among 505 patients who underwent liver transplantation, 5 whose mean pulmonary artery pressure > 45 mm Hg were enrolled. The enrolled patients comprised 4 males and 1 females. While 2 of 5 patients received cadaveric livers, the other 3 were living donor transplants and one of them was pediatric. The patients' demographic variables including mean age (years), BMI (kg/m2), gender, ASA-MELD scores, comorbid diseases, and etiology of liver disease are presented in Table 2.

All 5 patients received pulmonary vasodilator therapy during operation. Because of the therapeutic potential of inhaled NO as a selective pulmonary vasodilator, it was used for all patients perioperatively in combination with sildenafil. The bridging therapy and intraoperative PAH therapy used are shown in Table 3.

As a routine practice in our clinic, intraoperative cell salvage was used for autologous blood transfusion. Patients' intraoperative blood

product and inotrope/vasopressor usage, duration of anhepatic phase and surgery are shown in Table 4.

mPAP values obtained at baseline, following bridging therapy, and at postoperative first month control are provided in Figure 1. Length of hospital/intensive care unit stay, duration of follow-up and mortality are shown in Table 5. While there was no perioperative mortality, on the sixth postoperative day one patient had atrial fibrillation and was treated with electrical cardioversion; further follow-up was uneventful. During our follow-up only 1 patient died 3 years after transplantation due to coronary artery disease.

Table 3. Bridging therapy and intraoperative PAP management of the patients

| | Bridging therapy | Perioperative management |
|---|---|---|
| Patient1 | Bosentan, Sildenafil | Inhaled NO + Sildenafil |
| Patient2 | Bosentan (unresponsive) Sildenafil, Ambrisentan | Inhaled NO + Sildenafil |
| Patient3 | Sildenafil | Inhaled NO + Sildenafil |
| Patient4 | Sildenafil | Inhaled NO + Sildenafil |
| Patient5 | Bosentan, Sildenafil | Inhaled NO + Sildenafil |

Table 4. Intraoperative findings

| | ES (U) | TDP (U) | Platelet suspension (U) | Cryoprecipitate (U) | Vasopressor/ Inotrope | Anhepatic phase (min) | Surgery (min) |
|---|---|---|---|---|---|---|---|
| Patient1 | 2 | 3 | - | - | Noradrenaline | 65 | 420 |
| Patient2 | 4 | 6 | 1 | 7 | Noradrenaline | 80 | 550 |
| Patient3 | 1 | - | - | - | Noradrenaline | 60 | 440 |
| Patient4 | 2 | 5 | 1 | 8 | Noradrenaline Dopamine | 75 | 480 |
| Patient5 | - | 1 | - | - | Noradrenaline | 50 | 350 |

Table 5. Postoperative follow-up findings

| | Length of hospital stay (day) | Length of ICU stay (day) | Duration of follow-up (month) | Mortality |
|---|---|---|---|---|
| Patient1 | 10 | 2 | 23 | No |
| Patient2 | 18 | 10 | 16 | No |
| Patient3 | 24 | 3 | 4 | No |
| Patient4 | 33 | 19 | 5 | No |
| Patient5 | 10 | 2 | 36 | Yes |

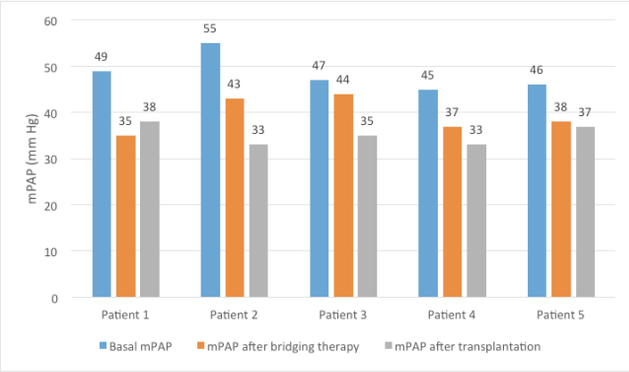


Figure 1. Mean pulmonary artery pressures (mPAP) of patients

## Discussion

Orthotopic liver transplantation (OLT) has significant success which in recent decades has turned the focus toward PoPAH that affect the survival with and without OLT. A clinical diagnosis of PoPAH can be made with the documentation of compatible hemodynamics in a patient with portal hypertension in the absence of coexisting conditions associated with pulmonary hypertension (11). In the setting of portal hypertension, PoPAH is diagnosed when mPAP of > 25 mm Hg, pulmonary vascular resistance (PVR) > 240 dynes.s.cm-5, and pulmonary artery wedge pressure (PAWP) < 15 mm Hg (12). It is vital to understand the disease, preoperative, and operative considerations for patients with PoPAH to deliver optimal care to this populations.

The role of liver transplantation in patients with severe PoPAH is still controversial and most of the unsuccessful surgical outcomes are based on case reports (13,14). In a retrospective study by Krowka et al., mortality after OLT was 100% for patients with PoPAH with mPAP greater than 50 mm Hg and 50% for those with mPAP 35 to 50 (15). So mPAP greater than 50 mm Hg was considered a contraindication in most transplant centers. On the other hand, some small studies and case series of patients with PoPAH, who responded to the vasodilatory or vasomodulating therapy and underwent OLT, had favorable post-transplant survival (16,17,18). Prostacyclin analogs, phosphodiesterase 5 inhibitors, endothelin receptor antagonists, and soluble guanylate cyclase stimulators are the main therapeutic agents targeting main pathways of pulmonary vasoconstriction in PoPAH (19). It is said that the better way to evaluate patients with moderate to severe PoPAH is whether they respond to bridging therapy. Most of the studies conclude that the patients can benefit from the liver transplant surgery when mPAP is lowered to < 35 mmHg. In our center 5 patients with severe PoPAH were treated with these agents preoperatively. Despite the fact that a definite decrease in mPAP was not observed in all patients, due to their partial response to bridging therapy, they were discussed extensively in a multidisciplinary transplantation council. Because a functioning liver graft has been shown to decrease mPAP (20,21) and the survival of these patients has significantly improved (21) due to advances in medical therapy, anesthesiology, and liver transplant surgery, they were encouraged to undergo liver transplantation.

Portopulmonary hypertension is usually asymptomatic and is known as a causative factor for mortality. While the most common symptom is dyspnea, orthopnea, chest pain, fatigue, syncope, and peripheral edema can be observed as the disorder progresses. In our patients dyspnea and fatigue were the most common symptoms.

In liver transplantation recipients, the prevalence of PoPAH increases to 4% to 8% (4,5,22). In some studies female sex and autoimmune hepatitis were found to be associated with PoPAH (23). In our study the prevalence of severe PoPAH was found to be 0.99% and it seems not to be related to the etiology and the female sex.

In a study by Starkel et al. only one of their 5 patients undergoing liver transplantation with severe PoPAH died, while the remaining 4 were alive and in excellent condition during the following 3 years (24). Similarly, in our study only one of 5 patients with severe PoPAH died while the others were alive at the time of our follow-up. Furthermore the patient who died 36 months after transplantation was the one who had the longest follow-

up and shortest ICU/hospital stay of the patients.

The limitations of our study are its retrospective design and lack of right heart catheterization (RHC) in 3 of 5 patients. It is recommended that in patients with moderate to severe pulmonary hypertension, RHC should be performed. Although it is a gold standard method for the diagnosis of PoPAH (25,26), in most trials as in ours, pulmonary artery pressure was obtained using Doppler TTE.

### *Conclusion*

We believe that liver transplantation should not be denied to all patients with severe PoPAH if they do not have right ventricular dysfunction. Given bridging therapy, advanced anesthetic and surgical management, patients with severe PoPAH can be considered acceptable for transplantation because recent data suggest that improvement or even cure of PAH in patients with end-stage liver disease seems possible through the transplantation. But it is obvious that these cases should be discussed in a multidisciplinary fashion and they should receive their treatment at an experienced center. Well-designed prospective studies are needed as well.

### *Scientific Responsibility Statement*

***The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.***

### *Animal and human rights statement*

***All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.***

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### *Conflict of interest*

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